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Third Annual International Umbilical Cord Blood Transplantation Symposium
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Symposium Summary

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The 31-member faculty for the Symposium included leaders of the major transplant centers in the United States, France, Japan, Spain, and Taiwan. Attendees included visitors from Japan, New Zealand, Australia, Singapore, France, the United Kingdom, Israel, Mexico, Columbia, Cyprus, Switzerland, India, Sweden, Italy, Taiwan, Kuwait, Saudi Arabia, the United Arab Emirates, Greece, Canada, Chile, Korea, and the United States.
The program was divided into 7 sessions: (I) umbilical cord blood transplantation (UCBT) in adults—current results and future directions; (II) infectious disease complications and immune reconstitution after UCBT; (III) approaches to augment the efficacy of UCBT; (IV) collection, processing, banking, thawing, and administration of umbilical cord blood (UCB) units—quality issues; (V) transplantation in children/genetic disorders; (VI) multipotent stem cells and regenerative medicine; and (VII) accreditation issues and the report from the Institute of Medicine. The following comments emphasize significant aspects of selected presentations. Further details are provided in the abstracts that follow.

Session I reviewed UCBT in adults.

A large majority of patients in need of hematopoietic cell transplantation are adults, and a significant body of data is accumulating regarding the effectiveness of UCB for this population. This is a most critical issue regarding the ability of UCB units to fulfill society's need for a source of stem cell products for all patients requiring a transplantation. The outcome results presented at the Symposium were highly encouraging.

Dr. Eliane Gluckman presented a Eurocord analysis of outcome results in 171 patients with hematologic malignancies who underwent transplantation after 1997. The median age of the patients was 29 years (range, 15-55 years), and the median follow-up time was 18 months (range, 1-71 months). At 2 years, disease-free survival for patients who underwent transplantation in the early, intermediate, and advanced phase of disease was 41% ± 9%, 34% ± 10%, and 18% ± 4%, respectively. Also, a matched-pair analysis was performed to compare the results of HLA-mismatched UCB and HLA-matched bone marrow transplantations (BMT) from unrelated donors in adults with acute leukemia. The 2-year cumulative incidences of chronic graft-versus-host disease (GVHD), transplant-related mortality (TRM), leukemia relapse, 2-year probability of survival, and leukemia-free survival were not significantly different.

A comparison was also performed with haploidentical related peripheral blood transplants. There were 220 patients with acute myeloid leukemia (AML) and 148 with acute lymphocytic leukemia (ALL), and these groups were analyzed separately. In those with AML, TRM (58% versus 46%)

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and the rate of relapse (24% versus 18%) were not different. In contrast, in those with ALL, the leukemia-free survival was higher in patients who received with UCB compared with haploidentical BMT (36% versus 13%). The difference was more significant in patients who underwent transplantation in second complete remission or more advanced disease.

These data suggest that, despite increased HLA disparity, UCB from unrelated donors offers results comparable to those with HLA-matched unrelated BMT in adults with acute leukemia. Therefore, the donor search process for bone marrow (BM) and UCB from unrelated donors should be started simultaneously in adults, especially in patients with acute leukemia, for whom time is very important. The choice of units containing a higher nucleated cell (NC) dose and a policy of earlier transplantation are likely to provide better results.

Dr. Pablo Rubinstein reported on the results of 1750 UCBTs performed since 1993 with units provided by the New York Blood Center. Of these, 396 recipients (22.6%) were ≥16 years old. Of the adults, 65% were ≥25 years old, 90% had hematologic malignancies, 33% had advanced disease (International Bone Marrow Transplantation Registry classification), 13% had received a prior autograft or allograft, and 11% received double-unit transplants. Engraftment was associated with the total nucleated cell (TNC) dose ($P = .004$) and HLA matching ($P = .003$), especially when recipients of transplants mismatched only in the graft-versus-host direction were counted as matched ($P = .001$). Significant differences in the probability of engraftment were also related to the conditioning regimens and to the use of double-unit transplantation. Within the adult group, age at transplantation was not significantly related to the probability of survival at 1 or 5 years. The difference in 1-year survival between recipients of grafts with <2.5 or $\geq 2.5 \times 10^7$ NCs per kilogram was not significant. The absence of HLA rejection mismatches was significantly associated with survival at 1 year (68% versus 27%; $P = .005$). Overall survival was 23% at 5 years. Engraftment and survival were significantly better in a group of 45 patients given a 2-unit transplant, most of whom also were treated with a fludarabine-containing regimen.

Dr. Satoshi Takahashi reported on results comparing UCBT and BMT at Tokyo University. Results indicate that UCBT from unrelated donors has efficacy comparable to that with BMT from unrelated donors and can restore hematopoiesis with acceptable toxicities in adults. He reported the clinical outcomes of 92 adult patients with hematologic malignancies (58% high risk) who received UCBT from unrelated donors after myeloablative conditioning. The median follow-up was 22 months (range, 1-82 months). The 1-year probability of TRM was 20%, and the 2-year probability of relapse was 18%. The 2-year probabilities of disease-free survival were 95% in standard-risk patients (n = 39) and 60% in high-risk adult patients (n = 53).

Dr. John Wagner reported on UCBT after nonmyeloablative therapy in 51 high-risk adults and adolescents with advanced hematologic malignancies. Approximately 1 in 4 (approximately 13 patients) received single and 3 in 4 (approximately 38 patients) received double UCB grafts. Units were predominantly 1- and 2-HLA antigen–mismatched with the recipient. Stratified into those with and without chemotherapy in the prior 4 months, the cumulative incidences of sustained donor engraftment were 98% and 64% ($P = .03$), respectively. The incidence of platelet recovery (50 000/μL) was 68%. The incidences of grade II to IV and grade III/IV acute GVHD were 63% and 25% at day 100, and the incidence of chronic GVHD was 28% at 1 year. TRM was 19% at day 180. Regression of relapsed or persistent disease has been seen in patients with myelodysplasia and intermediate- and low-grade lymphoid malignancies. The probability of overall survival at 1 year is 44%. Notably, only fitness, and not age, was associated with poor outcome. The data indicate that the regimen is well tolerated and sufficient for engraftment, particularly in patients with chemotherapy in the preceding 4 months. This approach extends access to transplantation to many adults who would otherwise be ineligible because of the lack of a donor or the inability to tolerate high-dose conditioning.

Dr. Haruko Tashiro presented data comparing the outcome in adult UCBTs between myeloablative and nonmyeloablative conditioning regimens. The myeloablative group consisted of 30 patients (median age, 33 years) with AML, ALL, non-Hodgkin lymphoma (NHL), myelodysplastic syndrome, and chronic myelogenous leukemia (CML). The nonmyeloablative group consisted of 22 patients (median age, 55 years) with AML, ALL, myelodysplastic syndrome, chronic myelomonocytic leukemia, NHL, Hodgkin disease, and chronic lymphocytic leukemia (CLL). The results indicated that the rate of engraftment failure, including conditioning failure and autologous recovery, was 27% in the myeloablative group and 32% in the nonmyeloablative group. Neutrophils were engrafted at day 23 and day 21 (median) in the myeloablative and nonmyeloablative groups, respectively. The cumulative incidence of grade III/IV acute GVHD was 26% in the myeloablative group and 40% in the nonmyeloablative group. The conclusion was that there were no significant differences in the probability of engraftment or in the duration to the engraftment of neutrophils between the 2 groups. The incidence of grade III/IV GVHD in the nonmyeloablative group was higher than that in the myeloablative group.

Dr. Juliet Barker presented results of UCBT of 16 adult patients (aged 37-67 years) with advanced or refractory follicular NHL (n = 7), CLL (n = 6), or mantle cell lymphoma (n = 3). A nonmyeloablative conditioning regimen was used. Thirteen had sustained donor engraftment. Grade II to IV acute and extensive chronic GVHD was seen in 12 and 6 patients, respectively. Four patients (3 with follicular NHL and 1 with CLL) have died with progressive disease, and 12 are alive in complete remission between 180 and 1214 days after transplantation. Two of the 3 patients with failure of donor engraftment were salvaged with a single cycle of cyclophosphamide, vincristine, and prednisone. The lack of intensive combination chemotherapy immediately before transplantation may have contributed to their risk for graft rejection. The conclusion reached was that these preliminary results in indolent NHL, including CLL and mantle cell lymphoma, are encouraging, with 12 of 16 patients in sustained complete remission. Prior therapy is likely an important factor in donor engraftment, and the incidence of severe GVHD has been low. Patient referral before the development of refractory disease should be considered.

Dr. John Wagner presented results of double UCBT in the setting of a myeloablative preparative therapy. Because recipients of $<2.5 \times 10^7$ NCs per kilogram have slow hematopoietic recovery and a significantly lower incidence of engraftment, 2 partially HLA-matched units were used to augment the cell dose. Thirty-one adult and adolescent patients with high-risk hematologic malignancies underwent transplantation with 2 partially HLA-matched UCB units after myeloablative conditioning. Patients had AML (n = 15), ALL (n = 12), CML (n = 3), or NHL (n = 1). The median total infused dose was 3.7×10^7 NCs per kilogram (range, 1.1-6.3) and 4.9×10^5 CD34 cells per kilogram (range, 0.9-14.5). All patients engrafted at a median of 23 days (range, 14-41 days), with 1 unit predominating. No factor predicted which unit would predominate. The incidence of platelet recovery (>50 000/μL) was 73% at day 180. The incidence of grade II to IV and III/IV acute GVHD was 65% and 17%, respectively, at day 100. Disease-free survival was 72% at 1 year for patients who underwent transplantation in complete remission, with no relapse in this cohort (median follow-up, 1.2 years). These data suggest that (1) double-unit UCBT is safe, with 1 unit predominating over time; (2) double-unit UCBT extends the application to nearly all adults and adolescents; and (3) survival exceeds historical data with a single UCB unit.

Dr. Manuel N. Fernandez reported the results of a novel approach to augment engraftment after unrelated single UCBT. The approach is the coinfusion of the best available UCB unit (<3/6 HLA mismatch and TNCs $>1.5 \times 10^7$/kg) and a limited number ($2\text{-}2.5 \times 10^6$/kg) of highly T cell–depleted ($CD3^+$ <10 000/kg) mobilized peripheral blood stem cells after a myeloablative conditioning regimen. Twenty-eight high-risk adult patients (median age, 30 years; range, 16-60 years) underwent consecutive transplantations. The median TNC of the transplanted UCB units was 2.37×10^7/kg (range, 1.31-3.70), and the median $CD34^+$ cell count was 0.11×10^6/kg (range, 0.035-0.37). The third-party donor cells infused consisted of $CD34^+$ (2.31×10^6/kg; range, 1.05-2.58) and $CD3^+$ (2.5×10^3/kg; range, 0.50-9.80). After a median follow-up of 10 months (range, 1-75 months) for all patients and 16 months (range, 3-75 months) for the 20 living patients (9 survived >2 years), the 4-year overall survival is 67% for the entire group and 86% for the 19 after exclusion of the 5 older than 40 years and the 4 with maternal haploidentical peripheral blood stem cells. This strategy makes UCBT feasible as a first choice for most patients of a wide age range and may allow additional immunotherapeutic maneuvers.

Session II reviewed infectious disease complications and immune reconstitution after UCBT.

Dr. Jo-Anne van Burik reviewed infectious complications after unrelated UCBT. The reports of several large series of patients were reviewed, as was the epidemiology of individual infections, including bacteria, tuberculosis, pertussis, herpes simplex virus, varicella-zoster virus, cytomegalovirus, and human herpesvirus (HHV)–6 infections. Of 362 UCB samples tested by polymerase chain reaction, none had cytomegalovirus, Epstein-Barr virus, HHV-7, or HHV-8, and 2 had HHV-6. Among patients who die, most studies indicate a 30% to 40% rate of infection. Bacterial infections often occur before engraftment and may lead to graft failure. Delayed recovery of the immune response among patients with GVHD leads to viral infections, including at later time points. The risk of serious infection in UCBT is comparable to that with unmanipulated marrow transplantation.

Dr. Mary Laughlin reviewed the incidence of and risk factors for early severe infections after UCB. Contributing factors to bacterial, viral, and fungal infections occurring during the first 100 days after unrelated UCBT share features common to those observed after allogeneic transplantation with conventional marrow or peripheral blood stem cell grafts from adult donors. These contributing factors include host variables (age and underlying disease), type of conditioning (ablative or reduced intensity), duration of neutropenia, acute GVHD incidence and severity, and receipt of corticosteroids. In addition, preliminary clinical data point to possible unique UCB graft features that contribute to infections at these early time points, including UCB stem cell and accessory cell populations. The graft cell dose may also affect the kinetics of myeloid and lymphocyte reconstitution.

Dr. Nelson Chao discussed immune reconstitution after UCBT and pointed out that recovery of immunity involves reconstitution of the innate and adaptive immune cells and their respective function. T-cell reconstitution early after UCBT involves expansion of UCB T cells that are infused with the stem cells. This first wave of T cells is a result of peripheral expansion in secondary lymphoid organs. After peripheral expansion, there is a slower second wave of donor-derived precursors that come from the engrafted donor cells. These cells traffic through the thymus and are educated there. T-cell receptor excision circles (single joint [sj] TRECs) are generated within the thymus and identify new thymic emigrants and those that have not divided. Measurements of TRECs, spectratyping of the T-cell receptor Vβ families, and extensive phenotypic analyses have allowed determination of the time course of T-cell reconstitution and of some of the factors that contribute to or detract from rapid recovery. T-cell recovery after UCBT occurs primarily through peripheral expansion of adoptively transferred donor T cells and results in skewing of the T-cell repertoire. The reappearance of sjTREC-containing cells after UCBT is associated with increasing numbers of phenotypically naive T cells, improved mitogen and recall antigen responses, and diversification of the T-cell repertoire. The delay in central T-cell recovery in adults relative to children may be due to differences in thymic function resulting from age-related atrophy, GVHD, or the pharmacologic effects of prophylaxis and treatment of GVHD.

Session III reviewed approaches to augment the efficacy of UCBT.

Dr. Bruce Blazar discussed the physiology of regulatory T cells and their role as a treatment modality. Regulatory T cells are a subpopulation of naive $CD4^+$ T cells that coexpresses CD25, the interleukin 2 receptor α chain, and exhibits potent suppressor activity. $CD4^+CD25^+$ cells play a vital role in the induction and maintenance of peripheral self-tolerance and the prevention of systemic autoimmune disorders, including autoimmune gastritis, intestinal inflammation, and autoimmune diabetes in diabetes-prone (nonobese diabetic) mice. $CD4^+CD25^+$ cells regulate T-cell alloresponses and tolerance induction. Depletion of $CD4^+CD25^+$ cells augments a mixed lymphocyte reaction culture, whereas adding a graded number of $CD4^+CD25^+$ T cells results in a dose-response reduction in alloproliferation. Supplementation of the donor graft with donor but not host $CD4^+CD25^+$ cells had a marked amelioration of GVHD lethality in multiple strain combinations. Because $CD4^+CD25^+$ cells are capable of suppressing both $CD4^+$ and $CD8^+$ T cells, it is reasonable to assume that $CD4^+CD25^+$ cells may be beneficial in suppressing host antidonor responses that can cause BM graft rejection. This has now been demonstrated by 3 separate groups by using distinct model systems. Recent studies have shown that UCB $CD4^+CD25^+$ cells are more readily isolated and more often lead to high levels of suppression as compared with adult peripheral blood mononuclear cells. These preliminary findings demonstrating a high degree of mixed lymphocyte reaction suppression now have been extended in subsequent studies, with >100 UCB lines generated to date. Thus, the stage is set for clinical trials of $CD4^+CD25^+$ cells for GVHD inhibition and therapy and for engraftment promotion.

Dr. Elizabeth Shpall discussed transplantation of ex vivo–expanded UCB. She reported a study of 43 patients in whom ex vivo expansion of UCB was done in an attempt to improve time to engraftment and reduce the graft failure rate in the recipients. A fraction of each patient's UCB allograft was CD34-selected and cultured ex vivo for 10 or 14 days before transplantation in defined media with stem cell factor, granulocyte colony-stimulating factor, and megakaryocyte growth and differentiation factor. The remainder of the UCB graft was infused without further manipulation. This study demonstrated that CD34 selection and ex vivo expansion of UCB before transplantation is feasible. The engraftment failure rate was relatively low, and the time to neutrophil engraftment in large adults was in the range reported for pediatric recipients of much larger UCB cell doses. In a subsequent expansion trial, patients are now being randomized to receive either 2 unmanipulated UCB units or 1 unmanipulated unit plus 1 unit from which all the cells are expanded ex vivo. Another expansion trial technology involves the use of a copper chelating agent that has been shown to enhance the expansion of a more primitive $CD34^+$ UCB population when combined with early-acting growth factors.

Dr. Mary Laughlin reported transplantation outcomes for 2 adults with CML who received myeloablative conditioning followed by infusion of a nonexpanded single UCB graft containing a low mononuclear cell dose. These patients were enrolled in a supportive care clinical transplantation trial incorporating in vivo administration of recombinant human stem cell factor (R-MetHuSCF) and filgrastim administered concomitantly from the day of UCB infusion to the time of donor-derived hematopoietic recovery. Each patient engrafted promptly. The time to a donor-derived absolute neutrophil count >500/μL was 13 and 29 days. No adverse events attributable to R-MetHuSCF injections were observed. In vivo UCB expansion with administration of concomitant R-MetHuSCF and filgrastim may be an alternate strategy to facilitate prompt donor hematologic engraftment in adult UCBT recipients.

Dr. Juliet Barker presented the standard practice of selecting units that are HLA 4/6 to 6/6 matched with

the patient with cell doses that exceed 2.5×10^7 NCs per kilogram of recipient body weight. However, additional analysis of the outcome of US patients who underwent transplantation with a single-unit myeloablative conditioning demonstrated that a cell dose of $>2.5 \times 10^7$ NCs per kilogram is required for recipients of 5/6-matched units to achieve at least 50% survival at 1 year, whereas in 4/6 recipients the cell dose needs to exceed 5×10^7 NCs per kilogram to achieve a similar outcome. One possible strategy to improve adult UCBT outcomes is to use double unit grafts. This strategy for selection of 2 units thus far has included the requirement that all units contain at least 2.0×10^7 NCs per kilogram, and of those, the more closely matched units would be infused. The units must be no more than 2-antigen mismatched with the recipient and with each other, according to the current Minnesota protocol. Currently, it is reasonable for all patients to undergo a volunteer adult donor search and a UCB search at the time of referral. Donor choice will depend on patient diagnosis, the urgency of transplantation, the relative availability of an adequately matched volunteer donor versus a UCB unit of adequate dose and match, physician preference, and research priorities. A volunteer donor may be preferred for a patient with CML in chronic phase or early accelerated phase and possibly other diagnoses, such as myelofibrosis or severe aplastic anemia. If the transplantation is urgent, UCB is a clear advantage, although a volunteer donor could possibly be obtained by using a National Marrow Donor Program (NMDP) ultra urgent search strategy.

Dr. Hal Broxmeyer discussed strategies to improve homing of UCB stem cells as another approach to enhance engraftment in recipients of UCB. Not all mouse hematopoietic stem cells (HSCs) home with absolute efficiency. The chemokine stromal cell–derived factor–1 (SDF–1/CXCL12 and its Gα protein–linked 7 transmembrane–spanning receptor CXCR4 are involved in chemotaxis, mobilization, and homing of HSCs. CD26 is a cell-surface dipeptidylpeptidase IV that can truncate SDF-1/CXCL12. Inhibition or deletion of CD26 in target populations containing or highly enriched for human UCB and human and murine BM HSCs and hematopoietic progenitor/stem cells (HPCs) greatly enhanced the chemotactic responsiveness of these cells to SDF-1/CXCL12. Inhibition or deletion of CD26 in mice was associated with a greatly decreased ability to mobilize HPCs with granulocyte colony-stimulating factor. Recent work has found that in vitro inhibition of CD26 on human $CD34^+$ UCB cells enhances the engraftment of these cells in sublethally irradiated nonobese diabetic/severe combined immunodeficiency mice. These encouraging results with UCB cells suggest that targeting CD26 or other means of enhancing homing/engraftment may be of practical value in a clinical setting to use limiting numbers of UCB HSCs for successful transplantation.

Session IV reviewed collection, processing, banking, thawing, and administration of UCB units—quality issues.

Dr. Joanne Kurtzberg discussed the standardization of UCB banking procedures in the NMDP network, which functions as a program within the NMDP that uses common standards for UCB donors, collection, processing, and storage listing on a single registry in combination with volunteer adult donors.

Dr. Jeffrey McCullough discussed quality issues in UCB banking. Of 268 units of UCB shipped for transplantation to the University of Minnesota during a 3-year period, 151 (56%) had 1 or more issues potentially related to quality that required evaluation before a final decision regarding their suitability for use. There were 246 specific issues in 151 units. The issues involved quality control (54%), medical history (40%), and labels and documentation (6%). Risks to patients from these issues were judged to be likely in 10%, potential in 35%, and unlikely in 55%.

Dr. Rafael Bornstein presented data comparing precryopreservation and postcryopreservation $CD34^+$ counts from UCB units. An evaluation was performed at the Madrid Cord Blood Bank (MCBB) and at the University of Minnesota (UM) of 50 duplicate cryopreserved UCB aliquots (1.5-mL cryovials) from UCB units stored according to standard banking procedures. After shipment with a transport liquid nitrogen container, the aliquots were thawed and processed by the same protocol at both the UM and MCBB. Results were discrepant, but linear regression showed a significant relationship ($P < .001$), and it was possible to foresee with a confidence of 95% the thawed $CD34^+$ cell dose that would be infused to UCBT patients at the UM either from the prefreeze MCBB data or from the $CD34^+$ assessment with a cryopreserved aliquot. Whereas this regression model is specific for the UM and MCBB, the principle is that this approach could be widely applied to predict the transplantation outcomes from $CD34^+$ data provided by all UCB banks.

Dr. Emer Clarke discussed standardization of colony-forming cell assays. Previously published data have indicated significant variability in the quantification of hematopoietic progenitors by using the colony-forming cell assay. Two distinct proficiency-testing programs were designed to assess the contribution of various parameters to the variability. There were 54 participants in the first program and 134 in the second. The considerable increase in the coefficients of variation in the second test confirmed that sample-preparation steps contribute significantly to the variability in this assay. Standardized protocols for cell preparation and training will decrease this variability

and facilitate the global applicability of data generated from various laboratories.

Dr. Michael Creer discussed postthaw characterization of progenitor cell viability in UCB products. The significance of variations in the process of cryopreservation was evaluated, as was the significance of cell washing. The evaluation of cell washing indicated that cell washing to remove dimethyl sulfoxide, red blood cell stroma, and plasma after thawing is not necessary when UCB products are red blood cell–depleted and plasma-depleted before cryopreservation. At present, the only way to assess postthaw HPC functional viability is to measure colony-forming activity. Additional research needs to be performed to improve the standardization of measurements of colony-forming cell content and to identify potential alternative approaches to assess HPC functional viability with greater precision and correlation with transplantation outcome.

Session V reviewed transplantation of children/genetic disorders.

Dr. Joanne Kurtzberg discussed unrelated UCBT in pediatric patients with nonmalignant diseases, focusing on outcomes in 69 patients with inborn errors of metabolism who underwent transplantation between August 1999 and June 2004. The patients were diagnosed with mucopolysaccharidoses syndromes (57%), adrenoleukodystrophy (12%), metachromatic leukodystrophy (6%), Krabbe disease (23%), and Tay-Sachs disease. The cumulative incidence of overall survival was 80% (95% confidence interval, 71%-90%) and 72% (95% confidence interval, 61%-83%) at 180 and 365 days, respectively. Improved growth and cognitive function were seen in patients with Hurler syndrome and neonates with Krabbe disease.

Dr. Eliane Gluckman reported the results of several studies of UCBT in children. One study concerned 95 children who underwent UCBT for AML, and a second study concerned 195 patients who underwent transplantation for ALL. A third study concerned a multicenter retrospective analysis comparing the outcome of unrelated UCBTs (n = 99) with that of unrelated BMT (unmanipulated or T-cell depleted; n = 416) in children with acute leukemia. The results justify the simultaneous search for unrelated UCB and unrelated BM donors for children with acute leukemia. The decision to perform unrelated UCBTs will be based on the cell content of the graft, the number of HLA disparities, and the urgency of the transplantation.

Dr. Tang-Her Jaing reported on the outcome of unrelated UCBT in 9 young children with β-thalassemia major. Eight of the 9 patients are alive at median follow-up of 254 days after transplantation, with complete donor chimerism and transfusion independence. These results suggest that unrelated UCBT is an alternative treatment for young patients with transfusion-dependent thalassemia who lack an HLA-matched sibling donor. The high degree of success may relate to the fact that patients underwent transplantation at a young age, before complications of the disease developed (Lucarelli class I), and to the use of high cell doses.

Dr. David Jacobsohn discussed the outcomes of unrelated UCBTs (4/6-5/6 HLA matched) and allogeneic related hematopoietic BM or peripheral blood stem cell transplantations (6/6 HLA matched) in children with high-risk ALL. There were 23 matched sibling (20 BM and 3 peripheral blood stem cell) and 26 UCB recipients. TRM and GVHD were equal in both groups. The 3-year event-free survival was 60% in both groups. Age, sex, degree of HLA matching for UCB, and acute or chronic GVHD did not affect event-free survival. Thus, in pediatric patients with high-risk ALL in need of HSC transplantation, the outcome of matched-sibling HSC transplantation and UCBT is equivalent with regard to TRM, GVHD, and event-free survival. UCB should be considered a standard stem cell source to use in this group when a matched sibling is not available.

Dr. Demetrios Petropoulos presented favorable results in pediatric patients with advanced hematologic malignancies by using a reduced-intensity regimen of fludarabine 30 mg/m^2 intravenously for 4 days, melphalan 140 mg/m^2 intravenously for 1 day, and 9 Gy of total body irradiation in 3 single daily fractions of 3 Gy. GVHD prophylaxis consisted of tacrolimus and minimethotrexate.

Session VI reviewed multipotent stem cells and regenerative medicine.

Dr. Catherine Verfaillie discussed a population of primitive cells in normal human, rodent, and swine postnatal tissues that have, at the single-cell level, multipotent differentiation and extensive proliferation potential. These cells have been named multipotent adult progenitor cells. Improved isolation processes have now generated cells with Oct4 levels that vastly exceed the levels in multipotent adult progenitor cells previously published. This improvement has led to significantly greater differentiation ability and significantly greater in vivo engraftment ability.

Dr. Darwin Prockop discussed mesenchymal stem cells. Preparations of mesenchymal stem cells vary in quality from laboratory to laboratory; there is little, if any, standardization, and different results are obtained with cells called by the same names. A National Institutes of Health–sponsored effort is under way to develop and distribute standardized preparations of mesenchymal stem cells from marrow.

Dr. Curtis Cetrulo presented results on Wharton jelly as a source of multipotent mesenchymal cells with high telomerase activity that have the capability

to differentiate into bone, cartilage, muscle cells (cardiac), and nerve cells. The goal is to develop these cells as accessory supporting cells for UCBT.

Dr. Esmail Zanjani discussed the in vivo potential of human HSCs in a random-bred noninjury large-animal model in sheep. The plasticity potential of marrow, peripheral blood stem cells, and UCB stem cells was studied in vivo. Naturally occurring biological events in the early preimmune fetus include (1) developing sites for HSC engraftment, (2) large-scale HSC migration, (3) assimilation of donor HSCs, (4) a permissive tissue-specific environment, (5) high-level cellular proliferation in developing tissues and organs, and (6) immune naiveté. These events result in a reduced ability to reject human HSCs, permit the induction of donor-specific tolerance, and allow the long-term persistence of donor cells. These characteristics permit the detection of the full in vivo potential of human HSCs. Possible uses of the model include the study of in vivo activity of human HSCs, generation of donor-specific human cells, generation of donor-specific "humanized" organs, and generation of generic human cells or organs.

Session VII reviewed accreditation issues and the report from the Institute of Medicine.

Dr. Phyllis Warkentin discussed the NETCORD/Foundation for the Accreditation of Cellular Therapy (FACT) international UCB banking standards. She reviewed the history of FACT/NETCORD, the goals of the program, the standard-setting process, the scope of the standards, the accreditation program, and the inspections process and potential outcomes.

Dr. James McMannis reviewed the AABB standards and accreditation for UCB. For almost 60 years, the AABB has applied its extensive experience in standard setting, education, and accreditation programs to related biological therapies, including UCB collection and processing. Standards integrate quality-management systems with technical requirements and apply to donor selection, eligibility, product processing, storage, and issuance, including outcomes data collection. The AABB works closely with other organizations, eg, the Food and Drug Administration, International Society for Cellular Therapy, NMDP, FACT, and American Society for Blood and Marrow Transplantation, sponsoring joint educational programs and serving on joint committees. AABB believes that each organization brings specific experience and expertise to a national UCB program.

Dr. Richard Champlin reviewed the Institute of Medicine report on UCBT. In 2004, the US Congress appropriated $10 million for the establishment of a National Stem Cell Bank Program under the Health Resources and Services Administration. The Institute of Medicine was commissioned to review the use of UCB for stem cell treatment and make recommendations regarding a national system to support UCBT. The recommendations of the committee are included in a detailed report that is available to the public on the Internet at http://www.nap.edu/books/0309095867/html.